FDA U.S. FOOD & DRUG ADMINISTRATION

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Re: Docket Nos. FDA-2016-P-1874 and FDA-2017-P-3486

Dear Dr. Powell, Ms. Sorscher, Dr. Carome, and Dr. Hankin:

This letter responds to Public Citizen's citizen petition dated June 29, 2016 (Public Citizen Petition)[1] and BioMedEcon, LLC's citizen petition dated June 2, 2017 (BioMedEcon Petition).[2]

Public Citizen requests that the Food and Drug Administration (FDA, the Agency, or we) immediately require:

> (1) The addition of a boxed warning to the product labeling for all dopamine agonist drugs currently approved in the U.S. (apomorphine, bromocriptine, cabergoline, pramipexole, ropinirole, and rotigotine) describing the risk of developing certain impulse-control problems and compulsive behaviors, including pathological gambling, hypersexuality, compulsive shopping/spending/buying, and compulsive eating.
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> (2) Establish a risk evaluation and mitigation strategy (REMS) for dopamine agonists that includes the requirement that a "Dear Health Care Provider" (DHCP) letter be distributed to doctors and health care providers, and that a Medication Guide be distributed to patients with all new and refill prescriptions for dopamine agonist drugs. This DHCP letter and Medication Guide will warn doctors and patients about the risk of certain impulse-control problems and compulsive behaviors, and instruct them in appropriate measures to reduce the risk of developing such behaviors and to recognize and mitigate the harms from these adverse reactions when they occur.

(Public Citizen Petition at 1-2).

BioMedEcon requests that FDA require manufacturers of dopamine agonists currently approved for the treatment of moderate-to-severe Restless Legs Syndrome (RLS) (i.e., manufacturers of

[1] Docket No. FDA-2016-P-1874.
[2] Docket No. FDA-2017-P-3486.

pramipexole, ropinirole and rotigotine) to:

(1) Require a boxed warning to the labeling to advise of the important and serious risk for development of new onset and exacerbation of existing mental disorders;

(2) Require amendments to the Warnings and Precautions and Adverse Reactions sections of the product labeling to provide specific amplification of the risk to RLS patients for adverse mental disorder reactions;

(3) Require revisions to the current Medication Guide to more appropriately reflect the risk of serious adverse mental disorder events induced by dopamine agonist treatment for RLS; and

(4) Require issuance and dissemination of DHCP letters regarding the above labeling changes

(BioMedEcon Petition at 2-4).

For the reasons described below, the petitions' requests for boxed warnings, REMS, Medication Guides, and DHCP letters are denied. The BioMedEcon Petition is granted to the extent that FDA has determined that there is new safety information that should be included in the labeling for some of the dopamine agonists, and is notifying the relevant application holders for Mirapex (pramipexole dihydrochloride) (new drug application (NDA) 020667), Neupro (rotigotine) (NDA 021829), and Requip (ropinirole hydrochloride) (NDA 020658) that changes should be made to the language in the WARNINGS AND PRECAUTIONS, PATIENT COUNSELING INFORMATION, and PATIENT INFORMATION sections of labeling to clarify that patients may experience impulse control disorders (ICDs) and hallucinations/psychotic-like behavior while taking these products for the treatment of RLS. On our own initiative, we are also notifying application holders for Parlodel (bromocriptine mesylate) (NDA 017962), Dostinex (cabergoline) (NDA 020664) [3], and Cycloset (bromocriptine mesylate) (NDA 20866) that FDA has determined that there is new safety information regarding ICDs that should be included in the labeling for these dopamine agonists.

I. BACKGROUND

A. Dopamine Agonists

There are currently six FDA-approved drugs, that are the subject of approved NDAs, that constitute the dopamine agonist drug class: apomorphine, bromocriptine mesylate, cabergoline, pramipexole dihydrochloride, ropinirole hydrochloride, and rotigotine.[4] The proprietary names,

[3] In addition to the NDAs discussed, there are seven approved abbreviated new drug applications (ANDAs) for cabergoline: ANDAs 204735; 077750; 202947; 076310; 078035; 201503; and 077843.

[4] The Public Citizen Petition mentions partial dopamine agonist drugs (see Public Citizen Petition at 3). However, neither Public Citizen nor BioMedEcon makes requests regarding partial dopamine agonist drugs (e.g., aripiprazole and brexpiprazole). Therefore, this response does not address partial dopamine agonist drugs.

NDA numbers, and approved indications for these drugs are listed in Table 1, below:

TABLE 1. Dopamine Agonists, Associated NDA #'s, and Approved Indications

Active Ingredient	Proprietary Name	NDA #	Approved Indication(s)					
			Parkinson's Disease	Restless Legs Syndrome	Hyperprolactinemia-Associated Dysfunctions*	Acromegaly	Hypomobility	Type 2 Diabetes Mellitus
pramipexole dihydrochloride	Mirapex	020667	x	x				
pramipexole dihydrochloride	Mirapex ER	022421, 022514	x					
ropinirole hydrochloride	Requip	020658	x	x				
ropinirole hydrochloride	Requip XL	022008	x					
rotigotine	Neupro	021829	x	x				
apomorphine	Apokyn	021264	x				x	
cabergoline	Dostinex	*Discontinued: 020664*			x			
bromocriptine mesylate	Parlodel	017962	x		x	X		
bromocriptine mesylate	Cycloset	020866						x

*Dostinex (cabergoline) (NDA 020664) is indicated for the treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas. Parlodel (bromocriptine mesylate) (NDA 017962) is indicated for the treatment of dysfunctions of hyperprolactinemia including amenorrhea with or without galactorrhea, infertility, or hypogonadism, and is also indicated in patients with prolactin-secreting adenomas.

B. Impulse Control Disorders (ICDs)

Under the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, impulse control disorders (ICDs) constitute a group of psychiatric disorders involving problems in the self-control of emotions and behaviors. ICDs include compulsive gambling, buying, sexual behavior, and eating, and have been linked to the use of dopamine agonists.[5]

The ICDs associated with dopamine agonist drugs that are the primary focus of the Public Citizen Petition include pathological gambling, hypersexuality, compulsive shopping/spending/buying, and compulsive eating (Public Citizen Petition at 4). The ICDs associated with dopamine agonist drugs that are the focus of the BioMedEcon Petition include pathological gambling, hypersexuality, compulsive shopping, poriomania (wandering), binge eating, excessive masturbation, compulsive sexual behavior, kleptomania, and excessive sexual fantasies (BioMedEcon Petition at 3, 10, 11, 22). Various terminology is used to refer to these behaviors in the literature, including impulse-control problems, compulsive behaviors, and other

[5] Weintraub, D., et al. Clinical Spectrum of Impulse Control Disorders in Parkinson's Disease. Mov. Disord. 2015 Feb;30(2):121-7.

terms. When we refer to ICDs for purposes of this response, we are generally referring to the ICDs, impulse-control problems, and compulsive behaviors highlighted in the two petitions.

C. Other Adverse Mental Disorders

In addition to ICDs, addressed above, the BioMedEcon Petition discusses other adverse mental disorders that the petition asserts are associated with dopamine agonist drugs (BioMedEcon Petition at 2, 14). These disorders include mania, psychosis, and paraphilia (BioMedEcon Petition at 15).

D. Warnings in Prescription Drug Labeling

Subpart B of part 201 of title 21, Code of Federal Regulations, sets forth labeling requirements for prescription drugs including those related to content and format. For products described in § 201.56(b)(1),[6] FDA regulations at § 201.57 apply. Section 201.57(c)(6) states that the WARNINGS AND PRECAUTIONS section of a prescription drug's full prescribing information must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them, and steps that should be taken if they occur. Labeling must be revised to include a warning about a clinically significant hazard when there is reasonable evidence of a causal association of such an adverse event with the drug.[7]

For older drugs not described in § 201.56(b)(1),[8] FDA regulations for specific requirements on content and format of labeling for human prescription drug and biological products are at § 201.80.

FDA may require a boxed warning (sometimes referred to as a "black box" warning) under § 201.57(c)(1)[9] for certain contraindications or serious warnings, particularly those that may lead to death or serious injury. The boxed warning ordinarily must be based on clinical data. Whether to require a boxed warning is within FDA's discretion, and the agency exercises this discretion judiciously to preserve the impact and significance of boxed warnings.

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[6] Within the context of this petition response, these products include Mirapex, Mirapex ER, Requip, Requip XL, Neupro, Apokyn, and Cycloset.

[7] § 201.57(c)(6) & (7). See also, FDA's guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format Guidance* (October 2011), p. 3-5.

[8] Within the context of this petition response, these products include Parlodel and Dostinex.

[9] For older drugs not described in 21 CFR § 201.56(b)(1), special problems, particularly those that may lead to death or serious injury, may be required by FDA to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data. 21 CFR § 201.80(e).

As described in FDA's guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (October 2011) (Warnings Guidance),[10] a boxed warning ordinarily is used to highlight for prescribers one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug, OR
- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation), OR
- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if its distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) "Risk Evaluation and Mitigation Strategies" elements to assure safe use).[11]

Infrequently, a boxed warning may be used to highlight information that is especially important to a prescriber.[12]

E. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is a required risk management plan that can include one or more elements to ensure that the benefits of a drug outweigh its risks. Section 505-1 of the FD&C Act (21 U.S.C. 355-1) authorizes FDA to require a REMS if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug.

Section 505-1 also authorizes FDA to require holders of covered applications approved without a REMS to submit a proposed REMS if the Agency becomes aware of new safety information as defined in section 505-1(b)(3) and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

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[10] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended but not required.

[11] Warnings Guidance, p. 11.

[12] Id.

F. Medication Guides

A Medication Guide is FDA-approved patient labeling conforming to the specifications set forth in 21 CFR part 208 and other applicable regulations.[13,14] Per 21 CFR 208.1(b), the purpose of a Medication Guide is to provide information when FDA determines that it is necessary to patients' safe and effective use of drug products. FDA will require a Medication Guide if the Agency determines that one or more of the following circumstances exists:[15]

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

G. Dear Health Care Provider (DHCP) Letters

DHCP letters are correspondence, often in the form of a mass mailing from FDA or from the manufacturer or distributor of a drug, intended to alert physicians and other health care providers about important new or updated information regarding a drug.[16] In most cases, the information relates to an important safety concern that could affect the decision to use a drug or require some change in behavior by health care providers, patients, or caregivers to reduce the potential for harm from a drug.[17] Some DHCP letters are a part of REMS communication programs to inform intended target audiences about the implementation of a new or modified REMS or to present additional required safety information about the product.[18]

H. Labeling Changes Based on "New Safety Information"

Section 505(o)(4) authorizes FDA to require certain holders of approved applications for prescription drug products to make safety labeling changes if the Agency becomes aware of "new safety information" that FDA believes should be included in the drug's labeling. As defined in section 505-1(b)(3) of the FD&C Act, "new safety information" is information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the

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[13] 21 CFR 208.3(h).

[14] A Medication Guide can be required as part of a REMS or as a part of labeling but independent of REMS. See FDA guidance for industry, *Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* (November 2011).

[15] § 208.1(c).

[16] See FDA guidance for industry and FDA staff, *Dear Health Care Provider Letters: Improving Communication of Important Safety Information* (February 2017).

[17] Id.

[18] Id.

postmarket risk identification and analysis system under section 505(k) of the Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug that the Agency has become aware of (that may be based on a new analysis of existing information) since the drug was approved.

II. DISCUSSION

The labeling of approved dopamine agonists currently warns prescribers and patients about the possibility of developing ICDs. Nevertheless, Public Citizen requests a boxed warning, REMS, Medication Guide, and DHCP letter "with respect to prescription dopamine agonist drugs to reflect current evidence that these drugs are associated with the development of certain impulse-control problems and compulsive behaviors, including pathological gambling, hypersexuality, compulsive shopping/spending/buying, and compulsive eating" (Public Citizen Petition at 1). Public Citizen argues that "[t]hese are serious adverse reactions that can be prevented or reduced in frequency and severity by appropriate use of these drugs and timely recognition by physicians and caregivers" (Id).

BioMedEcon requests a boxed warning, revised labeling, revised Medication Guide, and DHCP letter for dopamine agonists currently approved for the treatment of moderate-to-severe RLS (i.e., pramipexole, ropinirole and rotigotine). BioMedEcon states that there is evidence demonstrating "that the use of [dopamine agonists] for the treatment of RLS is associated with the development of new onset and the exacerbation of existing bipolar and related disorders; schizophrenia spectrum and other psychotic disorders; substance-related and addictive disorders; disruptive, impulse-control and conduct disorders; paraphilic disorders; and obsessive-compulsive and related disorders" (BioMedEcon Petition at 1). BioMedEcon argues that current labeling for dopamine agonists approved for the treatment of RLS "is grossly insufficient" in conveying these associations (BioMedEcon Petition at 1-2).[19]

To evaluate these requests, FDA conducted a comprehensive review, which included, among other things, the following: a literature review, review of adverse event reports, and discussion/analysis of the evidence.

The Agency conducted an extensive literature review. FDA collected scientific literature searches of multiple sources, including The PubMed, Embase, Web of Science, and Google Scholar databases, and constructed a database of 650 articles that could potentially inform our review (including the articles referenced in the petitions). FDA then conducted a detailed analysis of 53 articles, published since 2010, from observational studies of ICDs in patients with Parkinson's disease or RLS, including 28 studies presented by the petitioners. With respect to bromocriptine and cabergoline, indicated for hyperprolactinemia and prolactin-secreting adenomas, we reviewed the 12 articles that were referenced in Public Citizen's Petition and 62

[19] BioMedEcon states that in contrast to the Public Citizen Petition, the BioMedEcon Petition "pertains to the risk for serious adverse mental disorder reactions (including new onset and exacerbations of psychosis and mania) induced by pramipexole, ropinirole and rotigotine for the treatment of RLS." (BioMedEcon Petition at 1, footnote 3).

additional publications. We also conducted independent Medline searches of the published literature regarding an association of Cycloset or bromocriptine and ICDs in patients with diabetes.

To review adverse event reports, we conducted searches on the FDA Adverse Event Reporting System (FAERS) using multiple detailed search strategies. With respect to bromocriptine and cabergoline, we evaluated adverse event data from the original clinical trials for the approved dopamine agonists treatments for patients with hyperprolactinemia and prolactin-secreting adenomas. Regarding Cycloset, we reviewed all annual reports and Period Adverse Drug Experience Reports submitted by the applicant since approval and conducted independent searches of FAERS data to identify cases of impulse-control problems or compulsive behavior in association with Cycloset or bromocriptine in the treatment of patients with diabetes mellitus.

In the following, we first discuss the petitions' requests for the addition of a boxed warning regarding ICDs and then BioMedEcon's requests as they relate to other adverse mental disorders. Next, we discuss BioMedEcon's request for labeling changes and FDA's determination to require certain labeling changes. We then discuss the petitions' REMS, Medication Guide, and DHCP Letter requests.

A. Requests to Add a Boxed Warning

Public Citizen requests the addition of a boxed warning to the product labeling for all dopamine agonist drugs currently approved in the U.S. (apomorphine, bromocriptine, cabergoline, pramipexole, ropinirole, and rotigotine) describing the risk of developing certain ICDs, including pathological gambling, hypersexuality, compulsive shopping/spending/buying, and compulsive eating (Public Citizen Petition at 1). Public Citizen argues that the warnings currently included in the labeling of dopamine agonist drugs regarding ICDs are inadequate (Public Citizen Petition at 3).

Public Citizen claims that there is abundant evidence supporting the need for boxed warnings (Public Citizen Petition at 24) and asserts that its review of the literature found strong evidence for a causal association between treatment with dopamine agonists and the development of certain serious ICDs (Public Citizen Petition at 24). Public Citizen contends that evidence, derived from clinical data, establishes a clear causal association between dopamine agonists as a class and certain ICDs (Public Citizen Petition at 25).

BioMedEcon requests that boxed warnings for pramipexole, ropinirole, or rotigotine (dopamine agonists FDA approved for the treatment of RLS) advise of the important and serious risk for: a) development of new onset and b) exacerbation of existing mental disorders (BioMedEcon Petition at 2). BioMedEcon states that the boxed warnings should particularly note important and serious risks for the development and exacerbation of bipolar and related disorders; schizophrenia spectrum and other psychotic disorders; substance-related and addictive disorders; disruptive impulse control and conduct disorders; paraphilic disorders; and obsessive-compulsive and related disorders (id.)

1. Requests for a Boxed Warning Concerning ICDs

a. Public Citizen's Evidence for Dopamine Agonists' Association with ICDs

Public Citizen uses the following factors to assess evidence of a causal relationship between the use of dopamine agonists and certain ICDs, to conclude that there is a "clear causal association," which, according to Public Citizen, supports the addition of a boxed warning:

(1) Frequency of reporting ICDs in different subpopulations of dopamine agonists users and estimates of increased risk attributable to dopamine agonist use;

(2) Safety signals derived from studies of postmarketing adverse event reports;

(3) Increased rates of ICD-related adverse events in industry-sponsored randomized, controlled trials;

(4) Temporal associations between dopamine agonist use and development of ICDs;

(5) Biological plausibility (the mechanism of dopamine agonists in causing ICDs); and

(6) A dose-response relationship for dopamine agonist use and the risk of ICDs.

(Public Citizen Petition at 7-20).

Public Citizen states that this review "[takes] into consideration the FDA's framework for establishing causality" (Public Citizen Petition at 6). As reflected in the Warnings Guidance, factors that FDA considers in assessing whether there is reasonable evidence of a causal association between a drug and adverse event for purposes of including an adverse event in the WARNINGS AND PRECAUTIONS section of drug product labeling include: (1) the frequency of reporting; (2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials; (3) evidence of a dose-response relationship; (4) the extent to which the adverse event is consistent with the pharmacology of the drug; (5) the temporal association between drug administration and the event; (6) existence of dechallenge and rechallenge experience; and (7) whether the adverse event is known to be caused by related drugs. While this is not the standard by which FDA determines whether an adverse event should be included as a *boxed warning* in labeling, we nevertheless reviewed the evidence according to Public Citizen's framework to correspond to the structure of their presentation.

Using Public Citizen's framework, we review the evidence that Public Citizen presented in support of their argument that there is reasonable evidence of a causal association between the use of dopamine agonists and certain ICDs, and that certain ICDs are a classwide side effect of dopamine agonist treatment (see Public Citizen Petition at 2, 7). Though we discuss the evidence using Public Citizen's framework, we note that causality is not the standard by which FDA determines whether to require a *boxed warning*, a REMS, a Medication Guide, or a DHCP Letter. We then apply the standards, included above, by which FDA determines whether to require a *boxed warning*, a REMS, a Medication Guide, or a DHCP Letter in addressing Public

Citizen's requests.

(1) Frequency of reporting ICDs in different subpopulations of dopamine agonists users and estimates of increased risk attributable to dopamine agonist use

Public Citizen asserts that there was significantly elevated prevalence of ICDs observed in patients taking dopamine agonists when compared with populations that had not been exposed, based on the great majority of studies they reviewed (Public Citizen Petition at 7). Public Citizen argues that many of these studies likely underestimate the true prevalence of ICDs (id.) Public Citizen also contends that studies have identified dopamine agonist exposure conferring at least twice but as much as 20 times increased risk of developing ICDs, when compared with populations that had not been exposed (id.)[20] Public Citizen argues that this suggests that the increased risk of developing ICDs is related to dopamine agonist drug exposure and is not an underlying risk of the disorder(s) the dopamine agonists are used to treat (id. at 11).

We agree that the literature describes ICDs as occurring frequently in patients treated with dopamine agonists. But we do not agree that, based on available ICD prevalence and risk literature, there is a sufficient basis to distinguish increased risk (if any) of developing ICDs that is directly related to dopamine agonist drug exposure from the pre-existing underlying risk of ICDs due to the disorder(s) itself.

A major portion of the clinical evidence cited by Public Citizen and that we found in our review comes from cross-sectional studies, which offer limited utility for risk assessment. The cross-sectional method identifies patients at a specific point or slice in time without regard to earlier or later events and lacks the capability to distinguish the temporal ordering of events (i.e., whether exposure to dopamine agonists preceded ICDs). The cross-sectional method also cannot quantify risk. Moreover, these studies relied on methods that make no distinction with respect to the spectrum of ICDs. We were also unable to quantify impulse-control related harms (e.g., incidence) from dopamine agonists in a clinically meaningful way.

The active questioning of patients is a method used to gain information about the frequency of ICDs (see Public Citizen Petition at 5). The questionnaire method for ICDs entails subjective interpretation, both by reporters and interviewers, which makes estimating prevalence of ICDs a challenge. It is possible for under-reporting, over-reporting, and biased reporting of ICDs to occur in studies that actively question patients about ICDs.

Weintraub, et al. cites epidemiological reviews suggesting that gambling (0.4 to 1.1%), compulsive buying (5.8%), compulsive overeating (2%), and compulsive sexual behavior (3-6%)

[20] See Perez-Lloret S, Rey MV, Fabre N, et al. Prevalence and pharmacological factors associated with impulse-control disorder symptoms in patients with Parkinson disease. Clin. Neuropharmacol. 2012;35(6):261-265. doi:10.1097/WNF.0b013e31826e6e6d.

all have a considerable background rate in the U.S.[21] Public Citizen provides additional references with similar figures.[22] It is plausible that this background risk is increased by dopamine agonist use in any patient population, however, there are a variety of other factors and associations, most of which were not considered by Public Citizen or by the studies we have examined, that have been correlated with the development of ICDs.

The uncontrollable confounding factors of individual biological susceptibility, the role of concomitant medication, unclear relationship of dose equivalence and biological potency among dopamine agonists, and the unclear denominator of use of a particular dopamine agonist in a particular patient population make it impossible at this time to discern the risk for ICDs in different subpopulations of dopamine agonist users.

(2) Safety signals derived from studies of postmarketing adverse event reports

Public Citizen states that important safety signals can be and have been gleaned from FAERS reports, and that one way to assess the strength of a safety signal using the FAERS database is to use proportional reporting ratios (PRR) (Public Citizen Petition at 11).

We agree that important safety signals can be and have been gleaned from FAERS data. However, neither the number of reports nor disproportionality measures such as PRR are an appropriate basis for assessing causality.[23]

Public Citizen refers to three peer reviewed publications that described the increased frequency of reports of certain ICDs with dopamine agonist use as providing evidence for a strong signal for ICDs (Public Citizen Petition at 11). Disproportionality measures (e.g., PRR) of spontaneous adverse event reports are appropriate for signal detection, but they must be followed by further assessment and cannot be the sole basis for assessing causality. Disproportionality analyses provide a statistical association between an event and a drug relative to other drugs in the same

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[21] Weintraub, D., et al. Clinical Spectrum of Impulse Control Disorders in Parkinson's Disease. Mov. Disord. 2015 Feb;30(2):121-7. doi: 10.1002/mds.26016.

[22] See Public Citizen reference nos. 26 (Voon V, Hassan K, Zurowski M, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology. 2006;67:1254-1257. doi:10.1212/01.wnl.0000238503.20816.13); 27 (Hodgins DC, Stea JN, Grant JE. Gambling disorders. Lancet. 2011;378(9806):1874-1884. doi:10.1016/S0140-6736(10)62185-X); 28 (Petry NM, Stinson FS, Grant BF. Comorbidity of DSM-IV pathological gambling and other psychiatric disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2005;66(5):564-574. doi:10.4088/JCP.v66n0504); 32 (McElroy SL, Keck PE, Pope HG, Smith JM, Strakowski SM. Compulsive buying: A report of 20 cases. J Clin Psychiatry. 1994;55(6):242-248); 33 (Weiss HD, Marsh L. Impulse control disorders and compulsive behaviors associated with dopaminergic therapies in Parkinson disease. Neurol Clin Pract. 2012;2(4):267-274. doi:10.1212/CPJ.0b013e318278be9b); 35 (Hudson JI, Hiripi E, Pope HG, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007;61(3):348-358. doi:10.1016/j.biopsych.2006.03.040); and 47 (Callesen MB, Scheel-Krüger J, Kringelbach ML, Møller A. A systematic review of impulse control disorders in Parkinson's disease. J Parkinsons Dis. 2013;3(2):105-138. doi:10.3233/JPD-120165).

[23] See FDA guidance for industry, *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005).

database. Such methods compare the observed count for a drug-event combination with an "expected" count in the databases. The "expected" count is based on the number of reports of the event for all other drugs in the database. Unexpectedly high reporting associations only signal that there may be an association between an adverse event and the drug.

Likewise, making inferences regarding causality based on the total number of spontaneous reports is not appropriate, as many factors can affect reporting. For example, media coverage is known to substantially stimulate adverse event reporting, including reports without sufficient information to be actionable.[24]

(3) Increased rates of ICD-related adverse events in industry-sponsored randomized, controlled trials

Public Citizen notes that the proportion of dopamine-agonist-exposed subjects reported to experience ICDs in industry-sponsored randomized controlled trials (RCTs) and open-label extensions is typically lower than prevalence or incidence reported in other peer-reviewed observational studies (Public Citizen Petition at 13). Public Citizen also notes that, in spite of the low number of cases of ICDs reported in industry-sponsored RCTs, the rates of ICDs are consistently numerically higher among subjects treated with dopamine agonists than those treated with a placebo (Public Citizen Petition at 16).

We agree with Public Citizen's conclusion that the incidence of ICD in controlled clinical trials is low. Further, even in these few instances, there were confounding variables, including instances where patients were enrolled in several of these trials and were also treated simultaneously with levodopa and other adjunctive medications for Parkinson's disease (e.g., amantadine, MAO-B inhibitors). Symptoms of ICDs were also encountered in patients taking placebos, albeit less frequently. This includes patients with early Parkinson's disease who were not taking any dopaminergic drugs.

These uncontrollable confounding factors make it difficult to come to any definitive conclusions concerning the causal association between the use of dopamine agonists and certain ICDs based on data from the industry-sponsored RCTs.

(4) Temporal associations between dopamine agonist use and ICDs

Public Citizen states that a temporal relationship between the use of dopamine agonists and the development of certain ICDs is additional evidence of a causal relationship (Public Citizen Petition at 16). Public Citizen argues that the presence of dechallenge examples (e.g., ICDs subsiding or stopping after discontinuing dopamine agonists) in particular provide strong evidence of a causal relationship between dopamine agonist use and the development of ICDs

[24] Hoffman KB, Demakas AR, Dimbill M, Tatonetti NP, Erdman CB. Stimulated reporting: The impact of US Food and Drug Administration-Issued Alerts on the Adverse Event Reporting System (FAERS). Drug Safety 2014; 37:971-980

(Public Citizen Petition at 17).

While we recognize the role of positive dechallenge as a factor in assessing whether there is a causal association between dopamine agonists and ICDs, a positive dechallenge by itself is not sufficient to establish a causal association. Case-report features that may suggest a causal association between the use of a product and the adverse event include the following:

- Occurrence of the adverse event in the expected time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy);
- Absence of symptoms related to the event prior to exposure;
- Evidence of positive dechallenge or positive rechallenge;
- Consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury;
- Consistency of the event with the known effects of other products in the class;
- Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies; and
- Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).[25]

There is inherent uncertainty in assessing whether improvements after discontinuing or decreasing the dose of dopamine agonists are due to these interventions or if they are merely coincidental. It is not possible to make clear statements that apply to groups of patients in a consistent fashion concerning when ICD might develop, at what dose, whether other medications contribute to the disturbance, or if the patient is at risk for such a syndrome. There are also examples in the Public Citizen Petition where ICDs persisted after cessation of dopamine agonists (see Public Citizen Petition at 17). Case reports in patients with hyperprolactinemia and/or prolactin secreting adenoma indicate that ICDs might affect both men and women, of any age, with micro- or macroprolactinomas at any stage of their treatment.[26] For these reasons, we do not agree with Public Citizen's implication that the existing dechallenge data constitute "strong evidence" of a causal association between ICDs and dopamine agonist use (Public Citizen Petition at 16). We conclude that the information presented in the Public Citizen Petition does not definitively establish a clear temporal relationship between the use of dopamine agonists and the development of certain ICDs.

[25] FDA guidance for industry, *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, pp. 6-7.
[26] Noronha S, Stokes V, Karavitaki N, Grossman A. Treating prolactinomas with dopamine agonists: always worth the gamble? Endocrine 2016; 51:205-210.

(5) Biological plausibility (the mechanism of dopamine agonists in causing ICDs)

Public Citizen contends that the literature provides evidence that the pharmacology of dopamine agonists leads to the development of ICDs and that for the purposes of drug labeling, this must be considered a class effect (Public Citizen Petition at 18-19).

We disagree with Public Citizen's conclusions regarding the biological plausibility of the conclusion that the pharmacology of dopamine agonists leads to the development of ICDs. Public Citizen's argument for biological plausibility focuses on the dopamine neuronal system that balances risk and reward in the brain and the various contributions of dopamine receptor subtypes to its pathological function. Public Citizen cites literature that hypothesizes that dopamine agonists differentially affect dopamine receptor subtypes and that this differential effect either produces the impulsive behavior or results in greater risk for ICDs. This argument is allegedly supported by *in vitro* and animal studies as well as neuropsychological studies in patients who are taking dopamine agonists. However, at least for Parkinson's disease, the role of the D_3 dopamine receptor subtype in causing impulsive behaviors in patients treated with dopamine agonist drugs remains mostly theoretical with conflicting information regarding the role D_3 receptors might have (if any) in development of ICDs.

In considering the biological plausibility that the mechanism of action of dopamine agonists leads to ICDs, it is worthwhile to consider the variety of biological, environmental, and exogenous factors that combine to create an individual's susceptibility to a behavioral disorder. In this regard, it is just as important to understand why most individuals taking dopamine agonists do not develop ICDs as it is to understand why some individuals do.

There is a wide range of risk factors and associations, other than dopamine agonist use, that have been correlated with the development of ICDs and related behaviors. These include demographic factors (e.g., country of residence, younger age, male sex (sexual behavior), and female sex (eating and buying behaviors)), neural substrate factors (e.g., imaging alterations in dopamine system, ventral striatum and cortex, and cognition (impairment in executive abilities and risk-reward processing)), clinical factors (e.g., levodopa use, amantadine use, early Parkinson's disease onset, and increasing severity of depression and anxiety), and premorbid factors (past or current history of cigarette smoking, personal or family history of gambling/alcoholism, personality traits (impulsivity/novelty seeking traits), and genetics (dopamine and glutamate system)).[27]

Public Citizen has in large measure not considered the contribution of factors outside of the realm of dopamine agonist use. For example, there is a relatively high prevalence rate for ICDs

[27] See Weintraub, D., et al. Clinical Spectrum of Impulse Control Disorders in Parkinson's Disease. Mov. Disord. 2015 Feb;30(2):121-7, doi: 10.1002/mds.26016, p. 123, Fig. 1 Correlates and potential risk factors for ICDs and related behaviors.

in the general population. Weintraub, et al. cites epidemiological reviews suggesting that gambling (0.4 to 1.1%), compulsive buying (5.8%), compulsive overeating (2%), and compulsive sexual behavior (3-6%) all have a considerable background rate in the U.S.[28]

An additional complicating factor in interpreting risk for ICDs associated with a specific drug class is the ubiquitous use of polypharmacy regimens (i.e., the concurrent use of multiple medications by a patient) for treating Parkinson's disease. These are often poorly described in case reports, and the contribution of underlying levodopa dose, anticholinergic treatment, amantadine and/or MAO-B inhibitor in confounding the risk or lowering the threshold for ICDs is unknown. In a patient receiving polypharmacy, the last drug added to the regimen will invariably be considered the culprit in generating an ICD when it is at least equally likely that the totality of pharmacological alteration of the basal ganglia / limbic system is at fault.

In sum, there are a variety of factors and associations, most of which were not considered by Public Citizen, that have been correlated with the development of ICDs. Biological plausibility is just one of those many risk factors. Although there is evidence dopamine agonists contribute to a biologically plausible mechanism, the role biological plausibility plays between dopamine agonist use and ICDs remains theoretical at this time.

(6) A dose-response relationship for dopamine agonist use and the risk of ICDs

Public Citizen states that the presence of a dose-response relationship, where patients taking higher doses have increased risk of the adverse event, provides further evidence in establishing causality (Public Citizen Petition at 19). Public Citizen also states that multiple studies have found evidence of a dose-response relationship for dopamine agonist exposure and the development of certain ICDs (id.) Public Citizen argues that based on the available data, it should be assumed that any exposure to dopamine agonist drugs confers an increased risk of developing certain ICDs (id. at 20).

In general, a dose-response relationship between a drug and an adverse reaction adds evidence of a causal relationship. However, we do not agree with Public Citizen's claim that the available data establishes a dose-response relationship between dopamine agonist use and the risk of ICDs.

After reviewing the literature, including the literature cited by Public Citizen,[29] we acknowledge

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[28] Weintraub, D., et al. Clinical Spectrum of Impulse Control Disorders in Parkinson's Disease. Mov. Disord. 2015 Feb;30(2):121-7. doi: 10.1002/mds.26016.

[29] See Joutsa J, Martikainen K, Vahlberg T, Kaasinen V. Effects of dopamine agonist dose and gender on the prognosis of impulse control disorders in Parkinson's disease. Parkinsonism Relat. Disord. 2012 Dec;18(10):1079-83; Perez-Lloret S, Rey MV, Fabre N, et al. Prevalence and pharmacological factors associated with impulse-control disorder symptoms in patients with Parkinson disease. Clin. Neuropharmacol. 2012 Nov-Dec;35(6):261-5; Callesen MB, Scheel-Kruger J, Kringelbach ML, Moller A. A systematic review of impulse control disorders in Parkinson's disease. J Parkinsons Dis. 2013;3(2):105-38. and Hassan A, Bower JH, Kumar N, et al. Dopamine agonist-triggered

the possibility that clinical experiences indicating ICDs from dopamine agonists requires exposures greater than "starting doses" or durations longer than a certain minimum. However, our literature review found only one study that used minimally acceptable methods to measure the relationship between time on dopamine agonist treatment and risk for ICDs.[30] This study found a constant risk for ICDs unrelated to the duration of dopamine agonist treatment.[31]

Dose-response relationships are more appropriately evaluated in the context of placebo-controlled, fixed-dose trials. It is difficult to reach conclusions regarding dose-response relationships from spontaneous reports.

Due to the limited data available, we are unable to determine whether there is a dose-response relationship between dopamine agonist drugs and ICDs.

Even taking all the above factors together, we do not agree with Public Citizen's conclusion that the evidence establishes a "clear causal association" between dopamine agonists and ICD . We interpret "clear causal association" to mean a well-defined quantitative understanding of the excess ICD risk specifically due to dopamine agonists. Our review did not identify any suitable scientific evidence about the frequency of ICD specifically due to dopamine agonists, as opposed to other related factors, such as the underlying disease process or concomitant treatments (see discussion in Section II.A.1.a.(1)).

Based on our review, while we do not agree that there is a "clear" or well-defined causal association between dopamine agonist use and ICDs, we do conclude that there is reasonable evidence of a causal association between dopamine agonists and ICDs. This supports that language in the WARNINGS AND PRECAUTIONS section of dopamine agonist product labeling concerning these adverse reactions must be included.

b. Public Citizen's Case Study Evidence Regarding Certain ICDs and Dopamine Agonists and Suggested Strategies for Prevention and Mitigation

(1) Public Citizen's Descriptions of Specific Instances of ICDs

In support of their requests for a boxed warning, Medication Guide, REMS, and DHCP letter, Public Citizen also presents a variety of case studies of individuals affected by ICD that were reported in peer-reviewed literature to demonstrate the seriousness of ICDs (Public Citizen Petition at 20-23). We have taken these examples into consideration in our analysis of the evidence supporting the petitions' requests.

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pathological behaviors: surveillance in the PD clinic reveals high frequencies. Parkinsonism Relat. Disord. 2011 May;17(4):260-4.

[30] Bastiaens J, Dorfman BJ, Christos PJ, Nirenberg MJ. Prospective cohort study of impulse control disorders in Parkinson's disease. Mov. Disord. 2013 Mar;28(3):327-33.

[31] Id.

(2) Public Citizen's Proposed Strategies for Reducing the Severity and Harm of ICDs

Public Citizen describes four characteristics that, if present, may put a patient at higher risk of dopamine agonist associated ICDs: age, anxiety or mood disorder, personal or family ICD history, and caffeine or cigarette use (Public Citizen Petition at 23-24). Public Citizen argues that patients who possess a number of these characteristics may wish to avoid dopamine agonist treatment (Public Citizen Petition at 24). Public Citizen further argues that, should a patient choose to proceed with dopamine agonist treatment, a patient possessing the four characteristics should be alerted that they are at particularly high risk and undergo enhanced monitoring (id.)

Taken as a whole, the four characteristics would not be useful discriminatory criteria because they include over half of the U.S. population.[32] Also, risk cannot be characterized for the individual patient (e.g. characterization of a patient as "high risk"), due to the variety of biological, environmental, and exogenous factors that combine to create an individual's susceptibility to the behavioral disorder. FDA generally requires labeling to include adverse reactions to inform patients and clinicians of the potential risks with a drug, and to provide mitigation strategies if there are any (e.g., reduce the dose or discontinue the drug).[33] We have determined that there is inadequate evidence to support requiring labeling changes concerning the four "higher risk" characteristics or the proposed "enhanced monitoring" measures that Public Citizen proposes.

We also do not agree that Public Citizen's proposed strategies to mitigate risk would necessarily prevent severe ICD outcomes with dopamine agonist treatment.

c. BioMedEcon's Evidence for ICDs and Other Adverse Mental Disorders Associated with Dopamine Agonists Indicated for RLS

BioMedEcon presents "factual grounds" for its requests as follows: 1) an overview of RLS; 2) a literature review; and 3) two retrospective claims analyses. The following presents our review of BiodMedEcon's support (i.e. "factual grounds") for its requests.

(1) BioMedEcon's RLS Overview

As part of its RLS overview, BioMedEcon presents information concerning the following:

- Clinical characteristics, pathophysiology, epidemiology, and burden of RLS;
- FDA-approved and guideline-recommended pharmacotherapy for RLS;

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[32] See Kessler, RC, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):617-27 doi: 10.1001/archpsyc.62.6.617; Mitchell, et al. Beverage caffeine intakes in the US Food. Chem. Toxicol. 2014 Jan;63:136-42. doi: 10.1016/j.fct.2013.10.042; and Jamal A, et al. Current Cigarette Smoking Among Adults — United States, 2005–2015. MMWR Morb. Mortal Wkly Rep. 2016;65:1205–1211. doi: http://dx.doi.org/10.15585/mmwr.mm6544a2.

[33] See Warnings Guidance.

- Mechanisms underlying the effectiveness of dopamine agonists for the treatment of RLS;
- Mechanisms undermining the effectiveness and tolerability of dopamine agonists: augmentation and dopamine agonist withdrawal syndrome;
- Mechanisms associated with the onset/exacerbation of dopamine-agonist induced adverse mental disorders; and
- FDA postmarketing surveillance of dopamine agonist-induced impulse control disorders among patients with RLS.

(BioMedEcon Petition at 7-13).

RLS is defined clinically by its cardinal symptoms:

- Urge to move the legs, often accompanied by leg discomfort;
- Rest worsens the urge to move;
- Getting up and moving improves the urge; and
- Evening or night worsens symptoms.[34]

- FDA-approved and guideline-recommended pharmacotherapy for RLS

Three dopamine agonist drugs (pramipexole, ropinirole, and rotigotine) are currently approved by FDA for the treatment of moderate-to-severe primary RLS. FDA's approval of these drugs specifically included a review of the evidence, in each case including adequate and well controlled clinical trials, in support of the drug's safety and efficacy.

- Mechanisms underlying the effectiveness of dopamine agonists for the treatment of RLS

BioMedEcon describes putative mechanisms underlying the effectiveness of dopamine agonists for the treatment of RLS, and selected treatment related adverse drug reactions: augmentation, dopamine agonist withdrawal syndrome (DAWS), and the onset or exacerbation of mental disorders (e.g., psychosis and ICDs) (see BioMedEcon Petition at 8-11). We acknowledge BioMedEcon's presentation of current scientific hypotheses about dopamine receptor subtypes, the relative affinities of dopamine agonists for these subtypes, and the mechanism of the generation of adverse treatment effects, however, these hypotheses remain theoretical and unproven. FDA generally relies primarily upon clinical trials data to describe the benefit associated with a given agent, independent of putative mechanisms of efficacy. In describing the balance of risk to benefit for a given drug, priority is given to the highest quality data available (e.g. data derived from randomized, well-controlled trials and robustly constructed epidemiological studies). We emphasize that our assessment of risk management strategies necessary to ensure that the benefits of a drug outweigh its risks does not depend upon a consideration of theoretical mechanisms of action.

[34] Earley, C. J. (2003). Restless legs syndrome. *New England Journal of Medicine*, 348(21), 2103-2109.

- Mechanisms undermining the effectiveness and tolerability of dopamine agonists

BioMedEcon describes an iatrogenic complication of dopamine agonist treatment known as "augmentation" (BioMedEcon Petition at 8). BioMedEcon states that augmentation, continuous long-term dopamine receptor stimulation by dopamine agonists, may ultimately worsen RLS symptom severity back to or even beyond the level experienced before dopamine agonist treatment initiation (id.) We acknowledge that there is medical literature that describes augmentation as an iatrogenic and at times profound worsening of RLS symptoms following persistent use of dopamine agonists.[35] However, it is unclear how augmentation, as presented by BioMedEcon, factors into the petitions' specific requests.

In addition, we did not find that BioMedEcon's discussion regarding DAWS, nor our review of the available information regarding DAWS, is relevant to the petitions' requests. BioMedEcon states that the mechanism by which DAWS occurs is similar to that of addiction and withdrawal of other drugs that also stimulate dopaminergic reward pathways, such as amphetamines and cocaine (BioMedEcon Petition at 10). However, this was a hypothesis put forth by the originators of DAWS and has never been subject to confirmation in either human investigation or animal models. Furthermore, the usual habit-forming and habit-maintaining behaviors of drug dependency, abuse (intentional non-therapeutic use), tolerance (tachyphylaxis requiring larger doses), and dependence with drug seeking behavior, have not been associated with DAWS. Given that a minority of patients receiving chronic dopamine agonist therapy develop DAWS, calling it a withdrawal syndrome confuses the true nature of the phenomenon.

While dopamine receptor stimulation is a part of addiction biology, it is only one piece in the long chain of events found in a complex biology. Accordingly, we do not find that the available evidence regarding augmentation or DAWS supports the petitioners' requests.

- Mechanisms associated with the onset/exacerbation of dopamine-agonist induced adverse mental disorder events

BioMedEcon argues that dopamine agonists used in combination with dopamine antagonists may induce or exacerbate psychoses (BioMedEcon Petition at 10). However, BioMedEcon does not provide clear support for this claim. Only a few cases of coincident use of dopamine agonists and antipsychotic agents have been described as provoking psychosis.[36] Moreover, there is no current treatment regimen that uses the combination of dopamine agonists and traditional dopamine blocking neuroleptics. Low dose atypical neuroleptic agents, such as olanzapine and quetiapine, have been used in Parkinson's disease patients with psychotic features, but evidence suggests that this is associated with worsening of the motor features of the disease and an

[35] Garcia-Borreguero, D. et al. Guidelines for the first-line treatment of restless legs syndrome/ Willis–Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Medicine 2016; 21, 1–11 http://dx.doi.org/10.1016/j.sleep.2016.01.017.

[36] The term psychosis here should not be confused with the occurrence of hallucination, which is well described and labeled for the dopamine agonist drug class.

increased risk of death in the elderly.[37] The prescribing information of both typical and atypical neuroleptics contains a boxed warning regarding the increased mortality in patients with dementia-related psychosis.[38] Also, the potential for drug interaction with levodopa and dopamine agonists is listed in the label of atypical antipsychotics.

Therefore, we did not find BioMedEcon's discussion regarding mechanisms associated with the onset/exacerbation of dopamine-agonist induced adverse mental disorder events relevant to the petitions' requests.[39]

- FDA postmarketing surveillance of dopamine agonist-induced ICDs among patients with RLS

BioMedEcon presents a review[40] of FAERS data in which investigators found high and statistically significant signals for dopamine agonists (BioMedEcon Petition at 11-13). As part of its review, BioMedEcon cites the investigators calculation of a PRR to assess the association between ICDs and dopamine agonists (see BioMedEcon Petition at 11).

As explained in our review of Public Citizen's presentation of safety signals derived from postmarketing adverse event report studies in Section II.A.1.a.(2) of this response, neither the number of reports nor disproportionality measures such as PRR can definitively establish a causal relationship. A careful review of all case reports' details is required to make informed assessments. However, we nevertheless took the FAERS data from both petitions as well as our own FAERS review into consideration when evaluating the petitions' requests.

(2) BioMedEcon's Literature Review

BioMedEcon presents a review of published case reports pertaining to new onset or exacerbation of existing mental disorders attributed to or possibly attributed to dopamine agonists among adult patients with RLS (BioMedEcon Petition at 14-21).

The majority of the references cited by BioMedEcon consist of published postmarketing case reports that are qualitatively similar to the FAERS reports that we assessed.[41] Most involve a

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[37] Fernandez, H. H., Trieschmann, M. E., & Friedman, J. H. (2003). Treatment of psychosis in Parkinson's disease. Drug safety, 26(9), 643-659.

[38] See, e.g., Label for Seroquel (quetiapine fumarate), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020639s066lbl.pdf.

[39] See, e.g., Label for Seroquel (quetiapine fumarate), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020639s066lbl.pdf.

[40] Moore TJ, Glenmullen J, Mattison DR. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. JAMA Internal Medicine. 2014;174(12):1930-1933.

[41] See Tippmann-Peikert M, Park JG, Boeve BF, Shepard JW, Silber MH. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. Neurology. 2007 Jan 23;68(4):301-3; Kolla BP, Mansukhani MP, Barraza R, Bostwick JM. Impact of dopamine agonists on compulsive behaviors: a case series of pramipexole-induced pathological gambling. Psychosomatics. 2010 May-Jun;51(3):271-3; Driver-Dunckley ED,

small number (1 to 3) of RLS patients treated with dopamine agonists who developed ICDs or other psychiatric adverse events. Also, most of the articles discussed cases reporting gambling disorders or other ICDs.[42] A small number of articles described cases of RLS patients who experienced psychosis, mania, or depression during treatment with dopamine agonists.[43] The clinical scenarios and level of evidence in the cases were similar to those in the FAERS reports assessed by FDA; some were identical cases. We took all the references cited by BioMedEcon into consideration as part of our review of both petitions' requests.

(3) BioMedEcon's Two Cohort Studies

BioMedEcon presents the results from two similarly designed matched new-user cohort studies conducted on behalf of Arbor Pharmaceuticals, the holder of gabapentin enacarbil (Horizant), an FDA-approved non-dopamine agonist treatment for RLS, to support its requests (see BioMedEcon Petition at 2, 22-24). The two BioMedEcon studies analyzed administrative healthcare claims in MarketScan Commercial and Medicare Supplemental (BioMedEcon Petition at 22-24). The first study measured associations between dopamine agonists and medical encounters for developmental disorders in RLS patients without preceding history of

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Noble BN, Hentz JG, Evidente VG, Caviness JN, Parish J, Krahn L, Adler CH. Gambling and increased sexual desire with dopaminergic medications in restless legs syndrome. Clin. Neuropharmacol. 2007 Sep-Oct;30(5):249-55; Quickfall J, Suchowersky O. Pathological gambling associated with dopamine agonist use in restless legs syndrome. Parkinsonism Relat. Disord. 2007 Dec;13(8):535-6; and Launois C, Leu-Semenescu S, Brion A, Arnulf I. Major depression after withdrawing dopamine agonists in two patients with restless legs syndrome and impulse control disorders. Sleep Med. 2013 Jul;14(7):696.

[42] See Tippmann-Peikert M, Park JG, Boeve BF, Shepard JW, Silber MH. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. Neurology. 2007 Jan 23;68(4):301-3; Kolla BP, Mansukhani MP, Barraza R, Bostwick JM. Impact of dopamine agonists on compulsive behaviors: a case series of pramipexole-induced pathological gambling. Psychosomatics. 2010 May-Jun;51(3):271-3; Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010 May;67(5):589-95; Quickfall J, Suchowersky O. Pathological gambling associated with dopamine agonist use in restless legs syndrome. Parkinsonism Relat. Disord. 2007 Dec;13(8):535-6; Evans AH, Stegeman JR. Punding in patients on dopamine agonists for restless leg syndrome. Mov. Disord. 2009 Jan 15;24(1):140-1; Evans AH, Butzkueven H. Dopamine agonist-induced pathological gambling in restless legs syndrome due to multiple sclerosis. Mov. Disord. 2007 Mar 15;22(4):590-1; Salas RE, Allen RP, Earley CJ, Gamaldo CE. Drug hoarding: a case of atypical dopamine dysregulation syndrome in a RLS patient Mov. Disord. 2009 Mar 15;24(4):627-8; Dang D, Cunnington D, Swieca J. The emergence of devastating impulse control disorders during dopamine agonist therapy of the restless legs syndrome. Clin Neuropharmacol. 2011 Mar-Apr;34(2):66-70; d'Orsi G, Demaio V, Specchio LM. Pathological gambling plus hypersexuality in restless legs syndrome: a new case. Neurol. Sci. 2011 Aug;32(4):707-9; and Jones HB, George S. 'You never told me I would turn into a gambler': a first person account of dopamine agonist--induced gambling addiction in a patient with restless legs syndrome. BMJ Case Rep. 2011 Aug 24;2011.

[43] See Perea E, Robbins BV, Hutto B. Psychosis related to ropinirole. Am J Psychiatry. 2006 Mar;163(3):547-8; Chopra A, Pendergrass DS, Bostwick JM. Mirtazapine-induced worsening of restless legs syndrome (RLS) and ropinirole-induced psychosis: challenges in management of depression in RLS. Psychosomatics. 2011 Jan-Feb;52(1):92-4; Bet PM, Franken LG, Klumpers UM. Could pramipexole induce acute mania? A case report. Bipolar Disord. 2013 Jun;15(4):446-8; and Launois C, Leu-Semenescu S, Brion A, Arnulf I. Major depression after withdrawing dopamine agonists in two patients with restless legs syndrome and impulse control disorders. Sleep Med. 2013 Jul;14(7):696.

mental disorders. The second study aimed to measure this association in RLS patients with a preceding history of mental disorders.

We assessed these studies for internal validity and found serious risk of bias due to study design flaws in both studies.[44] Therefore, we were unable to take the results of these studies into consideration for the purposes of our review and decision making regarding the petitions' requests. The following discusses why we found serious risk of bias in both studies, and why we were unable to take the results of the two studies into consideration.

- First BioMedEcon Study

The first BioMedEcon cohort study compared the cumulative incidence for mental disorders in adult RLS patients with and without prescription claims for two dopamine agonists, pramipexole and ropinirole. BioMedEcon alleges that this study found "significantly increased risk of subsequently developing new-onset mental disorders" in RLS patients exposed to dopamine agonists as compared to controlled who did not receive dopamine agonists (BioMedEcon Petition at 23).

We used ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) to analyze the internal validity of the first BioMedEcon study.[45] ROBINS-I assesses risk of bias in seven domains. Following ROBINS-I principles, we assessed the first BioMedEcon study and found a serious risk of bias in two domains: confounding and patient selection. Information withheld by BioMedEcon precluded assessment in two other domains: the deviations from intended interventions and missing data. Finally, we found low or moderate risk of bias in the remaining three domains: classification of interventions, measurement of outcomes, and selection of the reported results. The significant problems that we identified in the study design of the first BioMedEcon study limits the valid inferences that are possible from reading the study results.

The first BioMedEcon study was found to be at serious risk of bias due to confounding because of absent study controls for RLS severity. A non-causal confounding variable partially or completely explains drug-outcome associations observed in patient populations. Confounding might occur, for example, when (1) the confounding condition occurs more frequently in a drug-exposed group, and (2) the confounding condition causes the outcome. For the first BioMedEcon study, confounding might have occurred if (1) physicians more often use dopamine

[44] The two BioMedEcon studies used nearly identical methods, thus the risks for bias apply to both studies. The first BioMedEcon study, completed in patients *without* evidence for pre-existing mental disorders, estimated the association between a dopamine agonist prescription and further mental disorders at odds ratio (OR) 2.0, 95% confidence interval, CI, 1.5-2.6. The second BioMedEcon study, completed in patients *with* evidence for pre-existing mental disorders, estimated the association between a dopamine agonist prescription and further mental disorders at OR 1.3, 95% CI 1.0-1.6. BioMedEcon reported results from the second study as a brief narrative, with only selected results highlighted.

[45] Sterne JAC, Higgins JPT, Elbers RG, Reeves BC, and The Development Group for ROBINS-I. Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I): detailed guidance, updated 12 October 2016. (Accessed at http://www.riskofbias.info on July 8, 2017.)

agonists to treat patients with more severe RLS, and (2) more severe RLS more often leads to mental disorders.

BioMedEcon may have observed a non-causal association between dopamine agonist use and mental disorders simply because both share associations with more severe RLS, rather than a causal association between dopamine agonists and mental disorders. We also found evidence for a possible two-fold causal association between RLS and depression.[46] Further, impaired sleep from more severe RLS plausibly explains associations observed in administrative healthcare claims between dopamine agonists and mental disorders.[47] For these reasons, we consider RLS severity an important confounding domain.

A diagnosis of RLS requires subjective interpretation of patient-reported symptoms. This subjectivity can lead to an erroneous (i.e., false positive) RLS diagnosis.[48] Accordingly, not all patients identified as having RLS by diagnostic code will have RLS. BioMedEcon's analyses used prescription claims for pramipexole and ropinirole to define two RLS cohorts, one exposed and the other not exposed to dopamine agonists. Therefore, two factors (a diagnosis of RLS and a specific treatment for RLS) defined the exposed cohort. Only one factor (a diagnosis of RLS) defined the unexposed cohort. As a result, the fraction with RLS is plausibly higher in the exposed cohort. Through a process similar to confounding through differences in RLS severity, a difference between cohorts with respect to the fraction with RLS could contribute to a non-causal association. These considerations explain our preference for studies that compare cohorts with exposure to different drugs for the same medical condition.[49] For example, a preferable study could compare cohorts exposed to either dopamine agonist or gabapentin enacarbil, a non-dopamine agonist drug also approved by FDA for RLS.

We also found a serious risk of bias in selecting patients. BioMedEcon restricted the unexposed (control) cohort to patients without prescription claims for pramipexole or ropinirole anywhere in MarketScan, before or after RLS index. BioMedEcon attempted to match each eligible RLS patient from the pramipexole or ropinirole new user cohort with one eligible RLS patient without any prescription claims (before or after RLS index) for pramipexole or ropinirole. The matching variables included: (1) age at RLS index, (2) sex, (3) U.S. geographical region, (4) Charlson Comorbidity Index, (5) employment status, and (6) "follow-up period."[50] Functionally, this

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[46] Szentkiralyi A, Volzke H, Hoffmann W, Baune BT, Berger K. The relationship between depressive symptoms and restless legs syndrome in two prospective cohort studies. Psychosom. Med. 2013;75:359-65; Li Y, Mirzaei F, O'Reilly EJ, et al. Prospective study of restless legs syndrome and risk of depression in women. Am J Epidemiol 2012;176:279-88.

[47] Yeh P, Walters AS, Tsuang JW. Restless legs syndrome: a comprehensive overview on its epidemiology, risk factors, and treatment. Sleep Breath 2012;16:987-1007.

[48] Id.

[49] See FDA guidance for industry and FDA staff, *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* (May 2013).

[50] Other sources in the BioMedEcon Petition suggest age matching ±6 months, geographical region matching in five categories (Northeast, North Central, South, West, and Unknown), Charlson Comorbidity Index (CCI) matching in two categories (CCI=0 vs. CCI>0), and employment status matching in two categories (full or part time vs. none).

restriction excluded initially unexposed patients who later started treatment with dopamine agonists from the study. Serious risk of bias becomes a concern when post-treatment selection associates with both initial treatment and outcome. This situation applies to the first BioMedEcon study if future dopamine agonist prescriptions are associated with patients more prone to mental disorders. Because of concerns about biased selection, we prefer cohort designs that use, (1) only information known at baseline to select patients for study and (2) data analytic approaches to account for changes in treatment after cohort entry.

Because of the serious risks to the internal validity of the first BioMedEcon study, we did not analyze other considerations of possible importance to external validity for this study. These other considerations include possible concerns about diagnostic codes in healthcare claims as valid indicators for mental illness. The significant problems that we did identify with the study design of the first BioMedEcon study limits the valid inferences that can be made from that study, and therefore we were unable to take the results of this study into consideration for deliberating the petitions' requests.

- Second BioMedEcon Study

The second BioMedEcon study, completed in patients with evidence for pre-existing mental disorders, estimated the association between a dopamine agonist prescription and mental disorder exacerbation at OR 1.27, 95% CI 1.04-1.55. This study's results were presented in the BioMedEcon Petition as a brief narrative, with only selected results highlighted (BioMedEcon Petition at 24).

Because of the second study's incomplete reporting, we were unable to complete a formal, detailed analysis of this study. Nonetheless, based on what was provided, we did not find that the second BioMedEcon study provided any compelling evidence in support of BioMedEcon's requests.

d. FDA's Determination that an ICD Boxed Warning is Not Warranted

As described in the Background section of this response and the Warnings Guidance, a boxed warning is ordinarily used to highlight for prescribers one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug

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BioMedEcon vaguely referred, without explanation, to calculating a "parallel surrogate date" and "parallel follow-up periods." For each patient in the exposed cohort, BioMedEcon calculated the number of days between RLS index and first dopamine agonist prescription. Presumably, BioMedEcon restricted matches to unexposed patients with at least the same number of days in follow-up after RLS index, with the start date ("parallel surrogate date") for ascertaining study outcomes delayed after the RLS index by an interval in time equivalent to the number of days between the RLS index and first dopamine agonist prescription for the dopamine agonist-exposed match. The abbreviated description of study methods created uncertainty for FDA, particularly in regards to the adequacy of study procedures for producing matched patients followed for study outcomes during comparable periods in calendar time.

(e.g., a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug OR

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation) OR
- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if its distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the FD&C Act "Risk Evaluation and Mitigation Strategies" elements to assure safe use).

There may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber.[51]

Whether to require a boxed warning is within FDA's discretion, and the agency exercises this discretion judiciously to preserve the impact and significance of boxed warnings. In short, the petitioners have not shown that a boxed warning is necessary under these circumstances. The petitions do not show ICDs associated with dopamine agonist drugs to be so serious in proportion to the potential benefit from dopamine agonists drugs that it is essential to consider them in assessing the risks and benefits of using dopamine agonist drugs. Likewise, the information in the petitions does not demonstrate ICDs associated with dopamine agonist drugs to be a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of dopamine agonists. Finally, the Agency did not approve these drugs with restrictions to ensure safe use. Absent additional evidence, the petitions have not demonstrated that the Agency should change its determination that a boxed warning on ICDs is not warranted.

We believe that current dopamine agonists product labeling, revised as specified in our SLC letters for Mirapex (pramipexole dihydrochloride), Neupro (rotigotine), Parlodel (bromocriptine mesylate) Dostinex (cabergoline), and Cycloset (bromocriptine mesylate), provide adequate information to prescribers concerning the risk for ICDs in patients treated with dopamine agonists

FDA-approved prescribing information is a summary of the essential scientific information needed for the safe and effective use of a drug.[52] The question is whether additional labeling information is needed to ensure that prescribers can use dopamine agonist products safely and effectively. We believe that the risk of ICDs is appropriately described in the current dopamine agonist product labeling, including as revised as specified in our SLC letters, and is well understood by both the medical and patient community (see discussion, *supra*).

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[51] Warnings Guidance, p. 11.
[52] 21 CFR 201.56(a).

2. BioMedEcon's Request for a Boxed Warning for Adverse Mental Disorders Other Than ICDs

In their petition, BioMedEcon requests that the Agency require manufacturers of all dopamine agonists approved for the treatment of RLS (i.e., pramipexole, ropinirole, and rotigotine) to require a boxed warning to the labeling to "advise of the important and serious risk for: a) development of new onset and b) exacerbation of existing mental disorders" (BioMedEcon Petition at 2). The petition requests that the boxed warning include language relating to mental disorders other than ICDs, specifically the development and exacerbation of bipolar and related disorders; schizophrenia spectrum and other psychotic disorders; substance use disorders; and obsessive-compulsive and related disorders (BioMedEcon Petition at 2).

a. BioMedEcon's Petition Does not Establish that a Boxed Warning Relating to Other Adverse Mental Events Is Appropriate

While we have carefully reviewed the information in BioMedEcon's petition, the evidence is insufficient to support requiring a boxed warning for any of the mental disorders discussed above. The Agency's determination on this issue remains unchanged for the same reasons discussed above -- that the petitions have not demonstrated that a boxed warning for ICDs should be placed on dopamine agonist labeling (discussed in Sections II.A.1 and II.B).

Thus, the arguments made in the petitions do not alter the Agency's determination that the dopamine agonist product labeling as revised per the SLC letters for Mirapex (pramipexole dihydrochloride), Neupro (rotigotine), and Requip (ropinirole), described below, adequately describe the risk of adverse mental disorders and provide adequate information for their safe and effective use for treating RLS.[53]

b. Warnings and Precautions: Current Labeling and Safety Labeling Change Letters Issued Today

With respect to adverse mental disorders, such as those that BioMedEcon raises, we have determined that in patients with RLS, there is reasonable evidence of a causal association between treatment with pramipexole, ropinirole, or rotigotine, and specific psychiatric adverse reactions already included in labeling. The WARNINGS AND PRECAUTIONS section of labeling for pramipexole, ropinirole, and rotigotine includes information on ICDs, as well as hallucinations and psychotic-like behavior. Current labeling includes these psychotic and psychotic-like adverse reactions in the WARNINGS AND PRECAUTIONS sections entitled: "Hallucinations and Psychotic-like Behavior" for pramipexole; "Hallucinations/Psychotic-like Behavior" for ropinirole; and "Hallucinations/Psychosis" for rotigotine. These are also described in the PATIENT COUNSELING INFORMATION section of labeling for these drugs. Additionally, rebound and augmentation are described in the WARNINGS AND PRECAUTIONS in pramipexole, ropinirole, and rotigotine labeling. These warnings exist

[53] See Section II.C. Labeling Changes for the revised labeling.

among other serious side effects that a healthcare provider should consider when prescribing pramipexole, ropinirole, or rotigotine for the treatment of RLS. These other events include sudden onset of sleep without warning, orthostatic hypotension and syncope, hyperpyrexia and confusion, and melanoma.[54]

In our review, we also found that there is reasonable evidence of a causal relationship between dopamine agonists and the emergence of mania in RLS patients. The current labeling for pramipexole, ropinirole, and rotigotine do not explicitly mention mania as a risk. However, many manifestations of ICDs resemble or overlap with features of mania, and numerous cases reported as ICDs involved RLS patients who appeared to have manic or hypomanic syndromes, rather than isolated ICD behavior.[55] In addition, mania can present with all of the adverse events described in the warnings regarding psychotic and psychotic-like symptoms: hallucinations, delusions, paranoia, agitation, aggression, and abnormal thinking. Thus, the SLC letters that were issued today require sponsors to revise pramipexole, ropinirole, and rotigotine labeling to add "mania" as one of the possible manifestations of abnormal thinking and behavior in the "Hallucinations and Psychotic-like Behavior" section of labeling under WARNINGS AND PRECUATIONS (see Section II.C Labeling Changes).

We did not find, however, reasonable evidence of a causal association between dopamine agonist treatment for RLS and the development of, or exacerbation of, the following mental disorders cited by BioMedEcon: schizophrenia spectrum disorders, substance use disorders, addictive disorders, disruptive disorders, conduct disorder, paraphilic disorders, and obsessive-compulsive disorder.[56] BioMedEcon did not provide adequate evidence, nor did we find evidence for a causal relationship in our search. Most of BioMedEcon's supporting evidence in the Petition's overview of RLS is specific to ICDs. Hence, we do not find that the WARNINGS AND PRECAUTIONS section of labeling for pramipexole, ropinirole, and rotigotine should contain information concerning these mental disorders.

B. BioMedEcon's Request to Require Manufacturers of Pramipexole, Ropinirole, and Rotigotine to Amend Current Product Labeling to Provide Specific Amplification of the Risk to RLS Patients for Adverse Mental Disorder Reactions

BioMedEcon requests that FDA require manufacturers of pramipexole, ropinirole, and rotigotine update the WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS sections of product labeling to more fully reflect published evidence of serious adverse mental disorder

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[54] Mirapex (pramipexole) label https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020667s036lbl.pdf; Requip (ropinirole) label https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020658s034lbl.pdf; Neupro (rotigotine) label https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021829s016lbl.pdf.

[55] American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (fifth edition). Washington, D.C.

[56] We note that there are confounding factors when analyzing a relationship between RLS, psychiatric disorders, and dopamine agonist drugs. Importantly, RLS patients have an increased background prevalence of psychiatric disorders compared to the general population, and RLS and related conditions can be induced or exacerbated by many commonly used psychotropic medications.

events associated with dopamine agonist treatment for RLS (BioMedEcon Petition at 2-3). BioMedEcon claims that the risk of dopamine agonist-induced serious adverse mental disorder reactions described in current product labeling predominantly refers to those occurring among patients with Parkinson's disease, and as a result RLS patients and their healthcare providers may erroneously assume that adverse reactions provided in current product labeling are principally limited to Parkinson's disease patients (BioMedEcon Petition at 2-3).

Our review, which included literature cited by BioMedEcon, did reveal new reports of ICDs and other adverse mental disorders in RLS patients treated with dopamine agonists approved for the treatment of RLS since these products were first approved. Based on our review, we concluded that there are reports of ICDs and other forms of abnormal thinking and behavior in patients treated with dopamine agonists for RLS, and it is necessary to broaden the language in the WARNINGS AND PRECAUTIONS section labeling for pramipexole, ropinirole, and rotigotine to include the possibility that ICDs and hallucinations/psychotic-like behavior may occur in patients treated with dopamine agonists for RLS. However, as further explained within this response, we did not find that the data supported the petitions' requests for a boxed warning, REMS, medication guide, or DHCP letter.

As described below, we have notified application holders of labeling changes that must be made for pramipexole, ropinirole and rotigotine in the WARNINGS AND PRECAUTIONS and PATIENT COUNSELING INFORMATION sections of labeling for pramipexole, ropinirole, and rotigotine to include the possibility that ICDs and hallucinations/psychotic-like behavior may occur in patients treated with dopamine agonists for both Parkinson's disease and RLS, or to remove language specifying a single indication if appropriate.

Therefore, BioMedEcon's request is granted to the extent that we have notified application holders of changes that must be made to the language in the WARNINGS AND PRECAUTIONS and PATIENT COUNSELING INFORMATION sections of labeling for pramipexole, ropinirole, and rotigotine be revised to state that patients may experience ICDs while taking these products for the treatment of RLS, in addition to Parkinson's disease. We also announced that we are requiring that corresponding changes, such as additions to the patient information section, be made to other parts of labeling as appropriate.

Our review of the available information concerning a possible association between dopamine agonists and ICDs and other adverse mental disorders confirmed the existence of new reports of ICDs and other adverse mental disorders.

C. Labeling Changes

Although the Petitioners have not demonstrated that a boxed warning should be required for the dopamine agonists, in reviewing the evidence presented by Petitioners and otherwise collected by FDA in conjunction with that review, we have found that there is reasonable evidence of a causal association between the dopamine agonists and ICDs and other psychiatric disorders. Accordingly, we are requiring safety labeling changes as described in this section.

Dopamine Agonists indicated for the treatment of RLS

In our review, we found reports of ICDs and other forms of abnormal thinking and behavior in patients treated with dopamine agonists for RLS, and have determined that broadening the language in the WARNINGS AND PRECAUTIONS section labeling for Mirapex (pramipexole dihydrochloride), Neupro (rotigotine), and Requip (ropinirole hydrochloride) to include the possibility that ICDs and hallucinations/psychotic-like behavior may occur in patients treated with dopamine agonists for RLS is appropriate. Corresponding changes should also be made to other sections of labeling, as appropriate.

We conclude that changes to clarify that ICDs and hallucinations/psychotic-like behavior may occur in patients being treated for RLS are not necessary for Mirapex ER (pramipexole dihydrochloride) (NDA 022421), Requip XL (ropinirole hydrochloride) (NDA 022008), and Apokyn (apomorphine hydrochloride) (NDA 021264) because they are only indicated for the treatment of Parkinson's disease or hypomobility associated with Parkinson's disease.

Dopamine Agonists indicated for the treatment of hyperprolactinemia and prolactin-secreting adenoma

Our review found evidence of an association between dopamine agonists Parlodel (bromocriptine mesylate) (NDA 017962) and Dostinex (cabergoline) (NDA 020664) and ICDs for the hyperprolactinemia and prolactin-secreting adenoma indications. Therefore, we have determined it is appropriate to revise the PRECAUTIONS and ADVERSE EVENTS sections of the Parlodel (bromocriptine mesylate) and Dostinex (cabergoline) labeling and to make corresponding changes to other sections of labeling to better align these products' labeling with that of other dopamine agonists.

Dopamine Agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Cycloset (bromocriptine mesylate) is a dopamine agonist used for this indication. Its labeling currently does not include language referencing ICDs in the WARNINGS AND PRECAUTIONS section. Neither Petitioner submitted information concerning the use of bromocriptine mesylate for type 2 diabetes mellitus and the risk of ICDs.

Our review revealed only one reported post-marketing case of ICD occurrence with one patient taking Cycloset (bromocriptine mesylate) (NDA 20866) for the treatment of type 2 diabetes mellitus. However, because there is reasonable evidence to suggest that there is a general, causal relationship between dopamine agonists and ICDs, the Agency has determined that Cycloset labeling should be revised to align with the labeling of other dopamine agonist products regarding warning language about ICDs.

Accordingly, we have notified the applicable application holders that we believe the new safety information should be included in the labeling as follows (the deleted language appears as

strikeout text and the added language appears in *underlined italics*):

1. Mirapex (pramipexole dihydrochloride)

5 WARNINGS AND PRECAUTIONS

5.3 Impulse Control/Compulsive Behaviors

Case reports and the results of a cross-sectional study suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, binge eating, and/or other intense urges and the inability to control these urges while taking one or more of the medications, including MIRAPEX, that increase central dopaminergic tone ~~and that are generally used for the treatment of Parkinson's disease~~. In some cases, although not all, these urges were reported to have stopped when the dose was reduced, or the medication was discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with MIRAPEX *for Parkinson's disease or RLS*. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking MIRAPEX.

5.4 Hallucinations and Psychotic-like Behavior

Postmarketing reports with medications used to treat Parkinson's disease *or RLS*, including MIRAPEX, indicate that patients may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior during treatment with MIRAPEX or after starting or increasing the dose of MIRAPEX. Other drugs prescribed to improve the symptoms of Parkinson's disease *or RLS* can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, *mania,* disorientation, aggressive behavior, agitation, and delirium.

17 PATIENT COUNSELING INFORMATION

Hallucinations and Psychotic-like Behavior

Inform patients that hallucinations and other psychotic-like behavior can occur. ~~and that~~*In patients with Parkinson's disease,* the elderly are at a higher risk than younger patients ~~with Parkinson's disease~~ [*see Warnings and Precautions (5.4)*].

PATIENT INFORMATION

unusual urges. Some people who take certain medicines to treat Parkinson's disease *or RLS*, including MIRAPEX, have reported problems, such as gambling, compulsive eating, compulsive buying, and increased sex drive.[57]

hallucinations and other psychotic-like behavior (seeing visions, hearing sounds or feeling sensations that are not real, confusion, excessive suspicion, aggressive behavior, agitation, delusional beliefs and disorganized thinking). *The chances of having hallucinations or other psychotic-like changes are higher in people taking MIRAPEX for Parkinson's disease who are elderly (age 65 or older).* ~~Your chance of having hallucinations and other psychotic-like behavior is higher if you are elderly (age 65 or older).~~

2. Requip (ropinirole hydrochloride)

5 WARNINGS AND PRECAUTIONS

5.4 Hallucinations/Psychotic-like Behavior

Postmarketing reports indicate that patients *with Parkinson's disease or RLS* may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior during treatment with REQUIP or after starting or increasing the dose of REQUIP. Other drugs prescribed to improve the symptoms of Parkinson's disease *or RLS* can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, *mania,* disorientation, aggressive behavior, agitation, and delirium.

5.6 Impulse Control/Compulsive Behaviors

Reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge or compulsive eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including REQUIP, that increase central dopaminergic tone ~~and that are generally used for the treatment of Parkinson's disease and RLS~~. In some cases, although not all, these urges were reported to have stopped when the dose was reduced, or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with

[57] The current language describing "unusual urges" in the PATIENT INFORMATION section of labeling for Requip and Neupro are not specific to either indication; therefore, there are no proposed changes to this section of labeling for these two products.

REQUIP *for Parkinson's disease or RLS*. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking REQUIP.

17 PATIENT COUNSELING INFORMATION

Hallucinations/Psychotic-like Behavior

Inform patients that they may experience hallucinations (unreal visions, sounds, or sensations), and that other psychotic-like behavior can occur while taking REQUIP. ~~The~~ *In patients with Parkinson's disease, the* elderly are at greater risk than younger patients ~~with Parkinson's disease~~. This risk is greater in patients who are taking REQUIP with L-dopa or taking higher doses of REQUIP and may also be further increased in patients taking any other drugs that increase dopaminergic tone. Tell patients to report hallucinations or psychotic-like behavior to their healthcare provider promptly should they develop *[see Warnings and Precautions (5.4)]*.

Impulse Control/Compulsive Behaviors

Advise patients that they may experience impulse control and/or compulsive behaviors while taking ~~1 or more of the medications (including~~ REQUIP~~) that increase central dopaminergic tone, that are generally used for the treatment of Parkinson's disease~~. Advise patients to inform their physician or healthcare provider if they develop new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with REQUIP. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking REQUIP *[see Warnings and Precautions (5.6)]*.

3. Neupro (rotigotine)

5 WARNINGS AND PRECAUTIONS

5.3 Hallucinations/Psychosis

Post-marketing reports indicate that patients *with Parkinson's disease or RLS* may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic behavior during NEUPRO treatment or after starting or increasing the dose of NEUPRO. Other drugs prescribed to improve the symptoms of Parkinson's disease *or RLS* can have similar effects on thinking and behavior. This abnormal thinking and behavior may consist of one or more of the following: paranoid ideation, delusions, hallucinations, confusion, *mania,* disorientation, aggressive behavior, agitation, and delirium. These various manifestations of psychotic behavior were also observed during the clinical development of NEUPRO for early- and advanced-stage Parkinson's disease and Restless Legs Syndrome.

5.6 Impulse Control/Compulsive Behaviors

Patients may experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while

taking one or more of the medications, including NEUPRO, that increase central dopaminergic tone ~~and that are generally used for the treatment of Parkinson's disease~~. In some cases, although not all, these urges were reported to have stopped when the dose was reduced, or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, or other urges while being treated with NEUPRO *for Parkinson's disease or RLS*. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking NEUPRO.

17 PATIENT COUNSELING INFORMATION

Hallucinations/Psychosis

Inform patients that hallucinations and other symptoms of psychosis can occur while taking NEUPRO. ~~and that~~*In patients with Parkinson's disease,* the elderly are at a higher risk than younger patients ~~with Parkinson's disease~~ *[see Warnings and Precautions (5.3)]*.

Impulse Control/Compulsive Behaviors

Advise patients that they may experience impulse control and/or compulsive behaviors while taking ~~one or more of the medications generally used for the treatment of Parkinson's disease, including~~ NEUPRO. Ask patients about the development of new or increased gambling urges, sexual urges, or other urges while being treated with NEUPRO. Advise patients to inform their physician if they experience new or increased gambling urges, increased sexual urges, or other intense urges while taking NEUPRO *[see Warnings and Precautions (5.6)]*.

PATIENT INFORMATION (for Restless Legs Syndrome)

hallucinations and other psychosis. *NEUPRO can cause psychotic symptoms including hallucinations (seeing or hearing things that are not real), confusion, excessive suspicion, aggressive behavior, agitation, delusional beliefs (believing things that are not real), and disorganized thinking. If you have hallucinations or any of these other psychotic-like changes, talk with your doctor right away.*

4. Parlodel (bromocriptine mesylate)

- Move the language regarding impulse control problems and compulsive behavior from the PRECAUTIONS Parkinson's Disease section to the PRECAUTIONS General section and revise to read:

PRECAUTIONS/General

There have been ~~Postmarketing~~ reports ~~suggest that patients treated with anti-Parkinson medications can experience~~ *of patients experiencing* intense urges to gamble, increased sexual

urges, intense urges to spend money uncontrollably, and/or other intense urges, *and the inability.* ~~Patients may be unable~~ to control these urges while taking one or more of the medications, *including Parlodel,* ~~that are generally used for the treatment of Parkinson's disease and~~ that increase central dopaminergic tone~~, including Parlodel~~. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending, or other urges while being treated with Parlodel *for Parkinson's disease or hyperprolactinemia-associated dysfunctions*. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Parlodel.

PRECAUTIONS/Parkinson's Disease

- Delete the language regarding impulse control problems and compulsive behavior from this section and move to the General section with revisions as noted above.

~~Postmarketing reports suggest that patients treated with anti-Parkinson medications can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, and other intense urges. Patients may be unable to control these urges while taking one or more of the medications that are generally used for the treatment of Parkinson's disease and that increase central dopaminergic tone, including Parlodel. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with Parlodel. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Parlodel.~~

PRECAUTIONS/Information for Patients

Patients and their caregivers should be alerted to the possibility that ~~they~~ *patients* may experience intense urges to spend money uncontrollably, intense urges to gamble, increased sexual urges, and other intense urges, and the inability to control these urges while taking Parlodel. *Advise patients and their caregivers to inform their healthcare provider if they develop new or increased uncontrolled spending, gambling urges, sexual urges, or other urges while being treated with Parlodel* [See **PRECAUTIONS**].

ADVERSE REACTIONS/Adverse Reactions from Postmarketing Experience

Psychiatric disorders: Confusion, psychomotor agitation/excitation, hallucinations, psychotic disorders, insomnia, libido increase, hypersexuality, *and impulse control/compulsive behaviors (including gambling, spending, and other intense urges).*

5. Dostinex (cabergoline)

PRECAUTIONS/Psychiatric

Impulse control/compulsive behaviors including ~~P~~pathological gambling, increased libido, and hypersexuality have been reported in patients treated with dopamine agonists including cabergoline. This has been generally reversible upon reduction of the dose or treatment discontinuation (See **Postmarketing Surveillance data**). *Prescribers should consider dose reduction or stopping the medication if a patient develops such urges while taking cabergoline.*

Information for Patients

*Patients should be alerted to the possibility that patients may experience intense urges to spend money uncontrollably, intense urges to gamble, increased sexual urges, and other intense urges and the inability to control these urges while taking cabergoline. Advise patients to inform their healthcare provider if they develop new or increased uncontrolled spending, gambling urges, sexual urges, or other urges while being treated with cabergoline [See **PRECAUTIONS**].*

ADVERSE REACTIONS/Post-marketing Surveillance data

Other events have been reported in association with cabergoline: *impulse control/compulsive behavior symptoms, including* hypersexuality, increased libido, and pathological gambling (See **PRECAUTIONS, Psychiatric**).

6. Cycloset (bromocriptine mesylate)

HIGHLIGHTS – Warnings and Precautions

Impulse control/compulsive behaviors: May occur. Ask patients or their caregivers about new or increased gambling urges, sexual urges, uncontrolled spending, or other urges while being treated with CYCLOSET. (5.X).

5 WARNINGS AND PRECAUTIONS

5.X Impulse Control/Compulsive Behaviors

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including bromocriptine, that increase central dopaminergic tone. In some cases, although not all, these urges were reported to have stopped when the dose was reduced, or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with CYCLOSET.

Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking CYCLOSET.

6 ADVERSE REACTIONS

6.2 Postmarketing Experience

Psychotic and Psychiatric Disorders

Psychotic disorders *and impulse control behaviors (including pathological gambling)* have been reported with bromocriptine *[see Warnings and Precautions (5.2, 5.X)]*. ~~Additionally, pathological gambling has been reported with bromocriptine used to treat patients with Parkinson's disease. To date, there have been no reported cases of psychoses or pathological gambling among the CYCLOSET-treated patients (N=2500) in combined Phase 2 and 3 controlled clinical trials of CYCLOSET.~~

17 PATIENT COUNSELING INFORMATION

Impulse Control/Compulsive Behaviors

Advise patients that they may experience impulse control and/or compulsive behaviors while taking CYCLOSET. Advise patients to inform their physician or healthcare provider if they develop new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with CYCLOSET [see Warnings and Precautions (5.X)].

These letters notifying the application holders of the required labeling changes described above are being issued based on our authority to require safety labeling changes under section 505(o)(4) of the FD&C Act. Under section 505(o)(4) of the FD&C Act, the application holders are now required, within 30 days following notification, either (1) to submit a supplement containing proposed labeling changes, or (2) to notify the Agency that they do not believe labeling changes are warranted and submit a statement detailing the reasons they believe such changes are not warranted.

D. Request for a REMS, Medication Guide, and DHCP Letters

Public Citizen argues that a REMS is necessary to ensure that the benefits of dopamine agonist drugs outweigh the risks of these drugs (Public Citizen Petition at 26). Public Citizen requests that the REMS include the requirement that a Medication Guide and DHCP letter that warns doctors and patients about the risk of certain ICDs, and instruct them in appropriate measures to reduce the risk of developing such behaviors and to recognize and mitigate the harms from these adverse reactions (Public Citizen Petition at 1-2).

BioMedEcon requests that FDA require manufacturers of pramipexole, ropinirole, and rotigotine

"revise the current Medication Guide to more appropriately reflect the risk of serious adverse mental disorder events induced by [dopamine agonist treatment] for RLS" (BioMedEcon Petition at 3). BioMedEcon also requests that FDA require these manufacturers to issue and disseminate a DHCP Drug Warning Letters apprising them of the labeling changes requested in the BioMedEcon Petition (BioMedEcon Petition at 3).

We have determined that a REMS, Medication Guide, and DHCP Letters concerning ICDs or other adverse mental disorders are not warranted for dopamine agonists.

1. REMS

Section 505-1 of the FD&C Act authorizes FDA to require a REMS if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug. The goal of risk mitigation is to preserve a drug's benefits while reducing its risks to the extent possible. For the majority of drugs, routine risk mitigation measures, such as providing health care providers with risk information through FDA-approved prescribing information, are sufficient to preserve benefits while minimizing risks.[58] FDA's determination as to whether a REMS is necessary for a particular drug is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case. In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.[59]

We have determined that a REMS is not necessary for the benefits of dopamine agonists to outweigh the risks, including any risk of ICDs or other adverse mental disorders.

For Parkinson's disease patients, dopamine agonists contribute materially to the function, comfort, and well-being of persons with an otherwise devastating motor dysfunction that prior to effective treatment resulted in progressive immobility and a shortened life expectancy. Additionally, while there are several different classes of drugs approved for the treatment of Parkinson's disease, there are only four drugs approved for the treatment of RLS. Three of these RLS drugs are dopamine agonists (i.e., pramipexole, ropinirole, and rotigotine). The fourth RLS drug is Horizant, a gabapentin prodrug marketed by Arbor Pharmaceuticals, the sponsor of BioMedEcon's cohort studies.

Dopamine agonists are first line therapy for treating hyperprolactinemia and prolactin-secreting adenoma. The treatment options for these indications are extremely limited and have significant risks associated with surgery to the patient, such as the risks of anesthesia.

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[58] See FDA Guidance for Industry, *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (April 2019).
[59] See id.

These considerations put even greater weight on the benefits side of the benefit-risk balance for dopamine agonists indicated for RLS, hyperprolactinemia, and prolactin-secreting adenoma. We have determined that a REMS is not necessary to ensure the benefits outweigh the risks of dopamine agonists.

2. Medication Guide

Per 21 CFR 208.1(b), the purpose of a Medication Guide is to provide information when FDA determines that it is necessary to patients' safe and effective use of drug products. FDA will require a Medication Guide if the Agency determines that one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.[60]

We have determined that none of these circumstances exist.

BioMedEcon requests that FDA require manufacturers of pramipexole, ropinirole, and rotigotine to revise "the current Medication Guide" to more appropriately reflect the risk of serious adverse mental disorder events induced by dopamine agonist treatment for RLS (BioMedEcon Petition at 3). Currently, there are not approved Medication Guides for pramipexole, ropinirole, or rotigotine. However, the labeling for pramipexole, ropinirole, and rotigotine does include a PATIENT COUNSELING INFORMATION section that includes language providing that the prescriber should advise the patient to read the PATIENT PRESCRIBING INFORMATION section of the labeling. The PATIENT COUNSELING INFORMATION and PATIENT INFORMATION sections of labeling include information concerning ICDs (described as "unusual urges" in PATIENT INFORMATION), and other adverse mental disorders (e.g., hallucinations and psychotic-like behavior).

As previously discussed, current labeling and labeling changes described in the SLC letters are sufficient for the safe and effective use of these drugs. For these reasons, we have concluded that it is not necessary to require additional FDA-approved patient labeling, such as a Medication Guide, to convey information directly to patients.

[60] 21 CFR 208.1(c).

3. DHCP Letter

In general, a DHCP letter is used to notify health care providers about important new or updated information about a drug. In most cases, the information relates to an important safety concern that could affect the decision to use a drug or require some change in behavior by health care providers, patients, or caregivers to reduce the potential for harm from a drug.[61]

In addition to statements in labeling for patients and prescribers, there is extensive information about ICDs on the American Parkinson's Disease Association and Parkinson's Disease Foundation websites.[62] A PubMed search for ICD and dopamine agonists returned 333 publications over the last 10 years and 488 publications for "Parkinson's disease impulse control disorders" during the same period. The earliest reports of pathological gambling in patients treated for Parkinson's disease were published in 2000.

We have determined that a DHCP letter is not necessary to inform health care providers or patients about the required labeling changes in the SLC letters. The risk of ICDs and other adverse mental disorders are already known and addressed in dopamine agonist labeling.

III. CONCLUSION

Based on the reasons described in this response, we are granting in part BioMedEcon's request that FDA require manufacturers of pramipexole, ropinirole, and rotigotine to amend current product labeling to provide specific amplification of the risk to RLS patients for adverse mental disorder reactions to the extent that our SLC letters require that the language in the WARNINGS AND PRECAUTIONS and PATIENT COUNSELING INFORMATION sections of labeling for pramipexole, ropinirole and rotigotine be revised to include the possibility that ICDs and hallucinations/psychotic-like behavior may occur in patients treated with dopamine agonists for RLS.[63] We deny all the other petitions' requests.

As with all drug products, we will continue to monitor the safety of dopamine agonists and take further action if we determine it is appropriate to do so.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

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[61] FDA guidance for industry and FDA staff, *Dear Health Care Provider Letters: Improving Communication of Important Safety Information* (February 2017).

[62] See https://www.apdaparkinson.org/what-is-parkinsons/symptoms/impulse-control-disorders/; https://parkinson.org/Living-with-Parkinsons/Managing-Parkinsons/Advice-for-the-Newly-Diagnosed/Why-Do-I-Keep-Doing-This-Impulsivity.

[63] Note that we are also revising the patient information sections of labeling, in accordance with the analysis above.